Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached is captioned **"VERSION WITH MARKINGS TO SHOW CHANGES MADE."**

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Rejection under 35 U.S.C. § 112- new matter

The Office Action states that claims 1, 3, 4 and 14 are rejected under 35 U.S.C. § 112 as containing subject matter which was not described in the specification in such a way as to reasonable convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Office Action asserts that the phrase "oocyte has undergone at least one cell division" in claims 1 and 15 has no support in the as-filed application and its insertion represents new matter. Applicants respectfully submit that the above phrase does not represent new matter.

The requirement for written description involves the question of whether the subject matter of a claim conforms to the disclosure of an application as filed. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." (In re Gosteli, 872 F.2d 1008, 1012). The subject matter of the claim need not be described literally (i.e. using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement (MPEP 2163.02). The mere inclusion of dictionary or art recognized definitions known at the time of filing would not be considered new matter (MPEP 2163.07(I)). Further, an application may incorporate the content of another document or part thereof by reference to the document in the text of the specification (MPEP 2163.07(b)).

Applicants claims are supported by the specification in several places, for example, a definition for oocyte activation found on page 5: "Activation of mammalian oocytes involves exit from meiosis and reentry into the mitotic cell cycle, and the formation and migration of pronuclei within the cell." Applicants assert that one of skill in the art understands that entry of a cell into the mitotic cycle involves a commitment of the cell to undergo at least one cell division and, as such, one of skill in the art would recognize that the phrase "reentry into the mitotic

cycle" supports "at least one cell division". This position is supported by the dictionary of "cell cycle" in Cancerweb's online medical dictionary (Exhibit 1, enclosed herewith), which states that "....the transition from G0 to G1 is thought to commit the cell to completing the cycle and dividing". Since entry into the cell cycle involves a transition from G0 phase (resting cells) to G1 phase (activated cells), entry into the cell cycle commits the cell to "completing the cycle and dividing". As such, the dictionary supports our assertion that "reentry into the mitotic cycle" supports "at least one cell division".

Applicants submit that they have more than met the requirements for written description in the subject patent application, and support for the phrase "oocyte has undergone at least one cell division" is unequivocally found in the application. Accordingly, the rejection of claims 1, 3, 4 and 14 under 35 U.S.C. § 112 may be withdrawn.

Rejections under 35 U.S.C. § 112- second paragraph (indefiniteness)

Claims 1, 3-5, 13 and 15 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which application regards as the invention. Specifically, the Office Action asserts that claims are rendered indefinite by repetitions of phrases containing "said oocyte", in several steps. Applicants respectfully traverse this rejection.

Claim 1 recites a method whereby an oocyte is contacted with an agent and maintained. Claim 5 recites a method whereby an oocyte is contacted with an agent and contacted with sperm. These rejected claims recite only one type of oocyte, and when "said oocyte" is recited in the claim the phrase refers to that oocyte. Applicants assert that claims 1 and 5 are not indefinite, that there is only one oocyte within the meaning of each claim, and, as such, the phrase "said oocyte" is very clear within the meaning of each claim.

Solely to expedite prosecution, claim 15 has been amended to recited that an oocyte that is contacted with sperm is an "inseminated" oocyte. Later in claim 15, the claim this oocyte is referred to as an "inseminated" oocyte. Applicants submit that this rejection has been addressed.

Accordingly, this rejection may be withdrawn for claims 1, 3-5, 13 and 15.

Claims 1, 5 and 15 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which application regards as the invention. Specifically, the Office Action asserts that claims are rendered indefinite with regard to measurement of oocyte activation. Applicants respectfully traverse this rejection.

Claims 1 and 15 have been amended to more particularly point out and distinctly claim the subject matter of the invention, and state that an oocyte that has undergone at least one cell division indicates that the oocyte is activated, as such, this rejection is believed to have been addressed.

As regards Claim 5, there is no "measuring" step recited in the claim, and applicants assert that no measuring step is necessary in order complete the claim. Claim 5 recites that an oocyte is contacted with a NOS inhibitor and contacted with sperm, and the contacting steps alone are sufficient for oocyte activation inhibition. Whether or not activation is measured is not relevant to the claim. As such, applicants assert that the meaning of claim 5 is clear with respect to measurement of oocyte activation: the measurement is not necessary.

Accordingly, this rejection may be withdrawn.

Claims 1 and 15 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which application regards as the invention. Specifically, the Office Action asserts that claims are rendered indefinite by the phrase: "maintaining step indicates that the oocyte is activated" because it is unclear what feature indicates oocyte activation in the maintaining step is intended.

Claims 1 and 15 have been amended to more particularly point out and distinctly claim the subject matter of the invention, and, as such, this rejection is believed to have been addressed by the amendment.

Accordingly, this rejection may be withdrawn.

Rejection under 35 U.S.C. § 102- US Patent 6,255,109

Claims 1, 3, 4 and 15 have been rejected under 35 U.S.C. §102(e) as being anticipated by US Patent 6,255,109 (the '109 patent). The Office Action asserts that the '109 patent discloses a method of promoting development of mammalian oocytes or activating oocytes that anticipates the claims. Applicants respectfully traverse this rejection.

Claims 1, 3, 4 and 15 are directed towards methods of activating an oocyte *in vitro*, wherein a non-activated oocyte is exposed to a modulator of NO levels and the oocyte undergoes at least one cell division. The method is performed in the absence of sperm (claim 1) or may performed with sperm (claim 15).

In making the above rejection, the Office asserts that the '109 patent discloses methods for modulating activation of oocytes, and cites table 1, column 5 line 12 and column 18 line 39 in support of the rejections. However, the '109 patent does not disclose a method that involves *oocytes*.

In column 5 of the '109 patent, the methods for preparing the materials for use in Examples 1-7 of the patent are described. The following passage states that that oocytes were collected, shipped, and inseminated in vitro after 22-24 hours of exposure to maturation medium.

> The bovine cumulus-oocyte complexes (COCs) used were collected in Madison, Wis. (BOMED, Inc.), and were shipped in 2-ml of maturation medium in a battery powered incubator via overnight express mail service. Oocytes matured during transit and arrived within 24 h after exposure to maturation medium, pre-equilibrated at 39.degree. C. in 5 % CO.sub.2 in air. At 22-24 h after exposure to the medium, the COCs were inseminated in vitro as described in J. Lim et al., "Intracytoplasmic glutathione concentration and the role of .beta.-mercaptoethanol in preimplantation development of bovine embryos," Theriogenology, 46, 429-439 (1996). At 18 h post-insemination, COCs were cultured in groups (30-35 embryos) in a 4-well multidish (Nunc, Roskilde, Denmark) containing 0.8-ml of mBECM-C. Embryos were dislodged from CGs at 36-48 h post-insemination.

As such, the oocytes used in the methods of the '109 patent are inseminated and are thus zygotes or early stage embryos. An oocyte that is inseminated is not an oocyte. Furthermore, because oocyte activation occurs in the minutes following insemination, the inseminated oocytes in the '109 patent are activated oocytes. This position is supported in at least one place of the

'109 patent specification, where the subject "oocytes" are referred to as "embryos" (e.g. in column 5 line 42), and in Table 1, where the subject "oocytes", even in the *absence* of SNP, develop into blastocyst embryos. Since an oocyte that is inseminated is not an oocyte, the '109 patent does not disclose an oocyte and cannot anticipate the claimed invention. Nevertheless, solely for the purposes of expediting prosecution and without any intention to acquiesce to the correctness of the rejection, claims 1 and 15 have been amended to recite a "non-activated" oocyte. Since the oocytes of the '109 patent are inseminated and hence activated, they cannot anticipate the claimed invention.

Applicants assert that the rejection of claims under 35 U.S.C. §102(e) over US Patent 6,255,109 has been addressed. Applicants respectfully request the withdrawal of this rejection.

Rejection under 35 U.S.C. § 102- Herrero

Claim 5 has been rejected under 35 U.S.C. §102(b) as being anticipated by Herrero. The Office Action asserts that Herrero discloses a method of inhibiting oocyte activation during activation with sperm and various nitric oxide synthase inhibitors. Applicants respectfully traverse this rejection.

Claim 5 of the instant application is a method for inhibiting oocyte activation during fertilization, which method involves contacting an oocyte with a nitric oxide synthase inhibitor and further contacting the oocyte with sperm.

Herrero describes a method involving contacting a sperm with a nitric oxide inhibitor, and testing the effects of the treated sperm on fertilization (see, e.g., the abstract of Herrero). Herrero does not teach the step of contacting an oocyte with a nitric oxide synthase inhibitor and, as such, cannot anticipate the subject matter of claim 5.

Applicants assert that the rejection of claim 5 under 35 U.S.C. §102(e) over Herrero has been addressed. Applicants respectfully request the withdrawal of this rejection.

Rejection under 35 U.S.C. § 103- US Patent 6,255,109 in view of Herrero

Claims 1, 3-5, 13 and 15 are rejected under 35 U.S.C. §103(a) over U.S. Patent No. 6,255,109 (the '109 patent) in view of Herrero. Specifically the Office Action asserts that the '109 patent discloses methods of modulating activation of oocytes with NO donors, which, when

combined with Herrero's inhibitors of NOS and maintaining oocytes until cell divisions have occurred, renders the claimed invention as obvious. Applicants respectfully traverse this rejection.

It is well understood that in order for a proper *prima facie* case to be established, a reference or combination of references must suggest all the claim limitations.

The rejected claims recite several methods each involving contacting a *non-activated* oocyte with a nitric oxide-modulatory agent.

The '109 patent, as established above, describes contacting an *inseminated* i.e. activated oocyte with a NO-modulatory agent. As such, the '109 patent fails to disclose or suggest a method involving contacting a *non-activated* oocyte with a nitric oxide-modulatory agent.

The Herrero reference, as established above, describes involving contacting *sperm* with a nitric oxide inhibitor. As such, the Herrero reference fails to disclose a method involving contacting a *non-activated oocyte* with a nitric oxide-modulatory agent.

As such, the cited references fails to disclose a method involving contacting a *non-activated oocyte* with a nitric oxide-modulatory agent and cannot be combined to make a *prima facie* case of obviousness. Accordingly the rejection of claims 1, 3-5, 13 and 15 under 35 U.S.C. §103(a) over U.S. Patent No. 6,255,109 (the '109 patent) in view of Herrero may be withdrawn.

Rejection under 35 U.S.C. § 103- Grumetto in view of Jawerbaum and U.S. 6,077,710

Claims 1, 3-5, and 13 stand rejected under 35 U.S.C. §103(a) as being obvious over Grumetto in view of Jawerbaum and US Patent 6,077,710 (the '710 patent). Specifically the Office Action asserts that the Grumetto and Jawerbaum methods of modulating activation of oocytes by contacting oocytes with modulators of NO levels prior to sperm addition, insemination and cell division, combined with the '710 patent disclosure that activation of mammalian oocytes is a function of calcium, renders the claims obvious to one of skill in the art. Applicants respectfully traverse this rejection.

It is well known that in order for a proper *prima facie* case to be made, a reference or a combination of references must teach or suggest all of the claim limitations, there must be a motivation to combine the references, and there must be some expectation of success in combining the references.

As will be demonstrated below, the references cited in the Office Action firstly do not provide disclose all the claim limitations and secondly cannot be combined with any expectation of success.

The references do not suggest all the claim limitations

Claims 1, 3, 4 and 15 are directed towards a method of activating an oocyte wherein the oocyte undergoes at least one cell division.

As established in the response to the previous Office Action, Grumetto and Jawerbaum do not disclose a method wherein an oocyte undergoes at least one cell division.

The '710 patent similarly does not disclose a method wherein an oocyte undergoes at least one cell division, and, as such, fails to meet the deficiencies of Grumetto and Jawerbaum. Accordingly, this rejection may be withdrawn for claims 1, 3, 4 and 15.

The Office Action states that since the cited references are considered to be within the same field of endeavor and seek to solve the same problems as the instant application and claims, and one of skill in the art is free to select components available in the prior art. Applicants assert that this statement is not relevant to the question of obviousness in this case: the cited references completely fail to teach a limitation of the subject claims, and, as such, cannot be used to establish a *prima facie* case of obviousness. Accordingly, with regard to claims 1, 3, 4, and 15, this rejection may be withdrawn.

Claim 5 recites a method of inhibiting oocyte activation during fertilization which involves contacting an non-activated oocyte with a nitric oxide inhibitor and sperm.

Grumetto represents a study of the potential role of NO on various aspects of calcium modulation in an ascidian oocyte. The method disclosed by Grumetto involve administering SNP (an NO donor) to ascidian oocytes and measuring some effects. Grumetto fails to disclose a method that involves contacting an non-activated oocyte with a nitric oxide inhibitor and sperm. The Office appears to assert that Figure 4 of Grumetto represents an example of modulation of NO levels or oocyte activation during fertilization in the presence of sperm. However, the Office appears to be mistaken in this assertion. Figure 4 of Grumetto merely represents measurement of NO levels at fertilization - they are not levels that are modulated by SNP or any other NO

modulatory agent. As such, Grumetto fails to teach a method involving contacting an non-activated oocyte with a nitric oxide inhibitor and sperm.

Jawerbaum, as the Office Action states, teaches various methods in the absence of sperm. As such, Jawerbaum also fails to teach a method involving contacting an non-activated oocyte with a nitric oxide inhibitor and sperm.

The '710 patent is cited in the Office Action for assertedly demonstrating that activation of oocytes is related to Ca^{2+} fluctuations in oocytes including mammalian oocytes belonging to various mammalian species. The '710 patent fails to disclose a method involving contacting an non-activated oocyte with a nitric oxide inhibitor and sperm. As such, the '710 patent fails to meet the deficiencies of Grumetto and Jawerbaum and the combination of the references cannot make the subject matter of claim 5 obvious. Accordingly, this rejection may be withdrawn for claim 5.

The fact that the cited references cannot be used to establish a *prima facie* case of obviousness is sufficient to over come the rejection. To the extent that a further discussion is believed necessary, the Examiner is respectfully referred to the following.

The references cannot be combined with any reasonable expectation of success

Even if the references could be successfully combined, they could not be combined to suggest the invention with any reasonable expectation of success.

The Office Action stated that our arguments in response to the previous Office Action were considered but not found convincing since the references by Grumetto teaches an induction of fertilization current or fluctuations of Ca^{2+} levels by modulation of NO level and the '710 patent teaches that activation of oocytes or reentry into mitotic cycle of mammalian oocytes is directly related to cellular activity which is a function of Ca^{2+} levels.

As is well established in the Courts[1] and in the MPEP teaches at § 2141.02, a *prima facie* case of obviousness can be rebutted if the applicant can show that that art teaches away from the claimed invention.

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[1] *In re Geisler*, 116 F.3d at 1469, 43 U.S.P.Q.2d at 1346:

> [A] prima facie case of obviousness can be rebutted if the applicant (1) can establish the existence of unexpected properties in the range claimed, or (2) can show that the art in any material respect taught away from the claimed invention.

Grumetto states that "The inward currents induced by SNP addition were however never followed by the contraction of the cortex and the production of the first polar body in ascidian oocytes, suggesting that production of the inward current by SNP is not sufficient for oocyte activation" at the end of column 1 on page 724 (emphasis added) . In other words, Grumetto teaches that SNP cannot be used for oocyte activation. These statements represents a very significant teaching away from the invention, and would lead one of skill in the art away from practicing the invention with a reasonable expectation of success.

Applicants further re-iterate their previous assertions that, at the time the application was filed, 1) no clear link between NO, Ca^{2+} and oocyte activation in mammals existed; 2) it was not clear that NO and Ca^{2+} are interchangeable for oocyte activation; 3) methods practiced on ascidian oocytes would not have been practiced on mammalian oocytes with any expectation of success and 4) there was absolutely no indication that NO was a regulator of oocyte activation in mammals. It was not until the publication of the Applicant's Nature paper that these pieces fell into place.

In a scientific field with so much uncertainty, why would one of skill in the art have any expectation that Grumetto's method could be modified to be used to activate an oocyte, especially when Grumetto himself states that NO modulators cannot be used for that purpose?

In summary, Grumetto cannot be combined Jawerbaum and the '710 patent to make the claimed invention because these references do not teach or suggest all of the claim elements. Even if they could be combined, the invention would not have been practiced with any reasonable expectation of success because Grumetto significantly teaches away from the invention and the relationship between NO and oocyte activation was completely unknown at the time of filing of the instant application.

Applicants submit that the rejection of claims 1, 3-5, 13 and 15 under 35 U.S.C. § 103(a) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Thus, if the art teaches away from the claimed invention, the *prima facie* case of

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN209.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: January 6, 2003

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obviousness is rebutted.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Pages 1, 5 and 15 are amended, as shown below:

1. **(amended)** A method of activating an oocyte *in vitro*, the method comprising:

contacting ~~**said**~~ **a non-activated** oocyte with nitric oxide (NO), an NO donor, nitric oxide synthase (NOS), or inducer of NOS; and,

maintaining said oocyte until the oocyte has undergone at least one cell division,

wherein said activation is performed in the absence of sperm and wherein ~~**said maintaining step**~~ **an oocyte that has undergone at least one cell division** indicates that the oocyte is activated.

5. **(amended)** A method of inhibiting oocyte activation during fertilization *in vitro*, the method comprising:

contacting ~~**said**~~ **a non-activated** oocyte with a nitric oxide synthase inhibitor; and

contacting said oocyte with sperm,

wherein said oocyte is inhibited from activation during fertilization *in vitro*.

15. **(amended)** A method of activating an oocyte *in vitro*, the method comprising:

contacting ~~**said**~~ **a non-activated** oocyte with nitric oxide (NO), an NO donor, nitric oxide synthase (NOS), or inducer of NOS;

contacting said oocyte with sperm **to make an inseminated oocyte**; and

maintaining said **inseminated** oocyte until the **inseminated** oocyte has undergone at least one cell division,

wherein ~~**said maintaining step**~~ **an inseminated oocyte that has undergone at least one cell division** indicates that the **inseminated** oocyte is activated.

cell cycle

<cell biology, molecular biology> The sequence of events between mitotic divisions. The cycle is conventionally divided into G0, G1, (G standing for gap), S (synthesis phase during which the DNA is replicated), G2 and M (mitosis).

Cells that will not divide again are considered to be in G0 and the transition from G0 to G1 is thought to commit the cell to completing the cycle and dividing.

(26 Mar 1998)

Previous: cell cloning, cell communication, cell compartmentation, cell count, cell culture
Next: cell cycle proteins, cell cycle restriction point, cell death